A Phase 3, Multinational, Randomized, Placebo-Controlled Study of ARRY-371797 in Patients with Symptomatic Dilated Cardiomyopathy Due to a Lamin A/C Gene Mutation

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In patients with symptomatic New York Heart Association (NYHA) Class II/III/IV dilated cardiomyopathy (DCM) in which mutations in the gene encoding the lamin A/C protein (LMNA) have been implicated:Primary Objective:* NYHA Class II/III patients only…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON55538

Source
ToetsingOnline

Brief title
Array 797 301

Condition

- Myocardial disorders

Synonym
Lamin A/C Gene Mutation, Symptomatic Dilated Cardiomyopathy

Research involving
Human

Sponsors and support

Primary sponsor: Array BioPharma Inc. (a wholly owned subsidiary of Pfizer Inc.)
Source(s) of monetary or material Support: Array BioPharma Inc.

Intervention

Keyword: Dilated Cardiomyopathy, gerandomiseerd, Placebo-Controlled

Outcome measures

Primary outcome

Primary Endpoint:

* NYHA Class II/III patients only: Change from baseline in 6MWT at Week 24

Secondary outcome

Secondary Endpoints:

1. NYHA Class II/III patients only: Change from baseline in 6MWT at Weeks 4 and

24

2. NYHA Class II/III patients only: Change from baseline in Kansas City

Cardiomyopathy Questionnaire (KCCQ) Physical Limitation (PL) and Total Symptom

Score (TSS) domains at Weeks 12 and 24

3. NYHA Class II/III patients only: Change from baseline in Patient Global

Impression (PGI) scores at Weeks 12 and 24

o Patient Global Impression of Severity (PGI-S)

o Patient Global Impression of Change (PGI-C)

4. NYHA Class II/III patients only: Change from baseline in N terminal

pro-brain natriuretic peptide (NT-proBNP) at Weeks 4, 12 and 24

5. HFS: gedefinieerd als de tijd vanaf randomisatie tot het eerste optreden van

elke gebeurtenis in de samenstelling van overlijden als gevolg van welke

oorzaak dan ook, of verergering hartfalen (HF-gerelateerde

ziekenhuisopname of HF-gerelateerd spoedeisende zorgbezoek).

7. OS

8. Safety as determined by:

o Incidence and severity of adverse events (AEs)

o Changes in clinical safety laboratory tests, vital signs and 12 lead

electrocardiograms (ECGs)

o Incidence and severity of ventricular or atrial arrhythmias detected

clinically using existing implantable cardioverter defibrillator (ICD)/cardiac

resynchronization therapy defibrillator (CRT-D) or other applicable device

interrogations at Weeks 12 and 24

Study description

Background summary

Lamins are critical protein components of the nuclear lamina, which lie between the inner nuclear membrane and the chromatin. They provide structural support for the cell nucleus, participate in many different nuclear processes, including chromatin organization, connecting the nucleus to the cytoplasm, gene transcription and mitosis. Mutations in the gene encoding the lamin A/C protein (LMNA) cause a variety of human diseases, known collectively as laminopathies. Dilated cardiomyopathy (DCM), which is also referred to as non-ischemic heart failure (HF) with reduced ejection fraction (HFrEF), is one of the more common phenotypes associated with LMNA mutations. Mutations in the LMNA gene are the second most common cause of familial DCM after those in titin (TTN) (Hershberger et al 2013) and account for up to 8% of all cases. Patients with LMNA-related DCM frequently suffer from atrioventricular conduction defects and have a significantly increased risk of sudden death due to ventricular arrhythmias (Hershberger et al 2013).
Currently, there is no effective, disease-specific treatment available for LMNA-related DCM. To date, treatment is limited to conventional therapies for DCM (angiotensin-converting-enzyme inhibitors or angiotensin 2 receptor blockers, beta blockers, aldosterone receptor antagonists and diuretics) which

are largely symptomatic and supportive. Progressive deterioration in left ventricular (LV) function and refractory HF symptoms are often treated with resynchronization therapy (bi ventricular pacing/ICD). In patients whose disease continues to progress in spite of aggressive cardiovascular (CV) management, cardiac transplantation may be considered.

Study objective

In patients with symptomatic New York Heart Association (NYHA) Class II/III/IV dilated cardiomyopathy (DCM) in which mutations in the gene encoding the lamin A/C protein (LMNA) have been implicated:

Primary Objective:
* NYHA Class II/III patients only: Evaluate the effect of ARRY 371797 (PF-07265803) on functional capacity (as measured by the 6 minute walk test [6MWT]) compared to placebo

Secondary Objectives:
* NYHA Class II/III patients only: Evaluate additional measures of efficacy of ARRY-371797 (PF-07265803) compared to placebo in the randomized period
* Characterize the plasma pharmacokinetics (PK) of ARRY 371797 (PF-07265803) and metabolites
* Evaluate the impact of ARRY-371797 (PF-07265803) on hospitalization-free survival (HFS) and overall survival (OS)
* Evaluate the safety of ARRY-371797 (PF-07265803) compared to placebo

Study design

This multinational Phase 3 study will evaluate the efficacy, safety and PK following treatment with ARRY-371797 (PF-07265803) compared with placebo (1:1 randomization) in at least 120 patients with NYHA functional Class II and III DCM secondary to LMNA mutations. NYHA functional Class IV patients (up to approximately 40) will also be enrolled (1:1 randomization) and will be assessed for overall safety and time from randomization to HF-related hospitalization or death due to any cause, in addition to PK and efficacy, if feasible.
The study will be conducted in 2 parts: a randomized, double-blind treatment period for at least 24 weeks, followed by an ARRY 371797 (PF-07265803) open-label treatment period. During the randomized, double-blind period, patients, Investigators, site personnel and the Sponsor personnel directly involved with the conduct of the study will remain blinded to assigned treatment, except for regulatory reporting requirements. Study drug treatment received in the randomized period will remain blinded for all patients until the database is frozen/locked, the primary analysis is performed (after all patients have the opportunity to be followed for at least 24 weeks), and a mature evaluation of HF-related hospitalization and all-cause mortality has

been completed, after which treatments will be unblinded and patients receiving placebo may initiate treatment with ARRY 371797 (PF-07265803) provided eligibility criteria are met. The end of the study is reached when all patients in the open-label treatment period have had the opportunity to be followed for at least 24 weeks in the open-label period of the study or have discontinued from the study, whichever comes first. Patients who remain on treatment at the end of the study and who may, in the opinion of the Investigator, derive benefit from continued treatment with ARRY-371797 (PF-07265803) will be provided the opportunity to continue treatment with ARRY-371797 (PF-07265803).
An independent Data Monitoring Committee (DMC) will review safety, PK and efficacy data at regular intervals. A study Steering Committee (SC) will be involved in oversight of the study and will ensure transparent management of the study according to the protocol. A Clinical Events Committee (CEC) will be utilized to adjudicate causes for hospitalizations.
For NYHA Class II/III patients, a central laboratory will be used for analyses of ECGs, echocardiograms (ECHO), NT-proBNP and safety laboratory assessments. For NYHA Class IV patients who are not able to attend post-baseline clinic visits, local laboratories may be used.
One formal interim efficacy analysis for futility will be performed on the Week 12 6MWT data after the first 30 randomized NYHA Class II/III patients have completed the Week 12 assessment or have discontinued from the study prior to Week 12.

Intervention

Patients will be randomized (1:1) to the following groups:
* ARRY-371797: 400 mg BID (4 × 100 mg tablets, BID)
(800 mg total daily dose)
* Matching placebo: 4 tablets BID (8 tablets daily)
Placebo and active drug tablets will be identical in appearance during the double-blind treatment period to maintain the study blind.

If a patient has safety or tolerability issues at 4 tablets BID (ARRY 371797 [400 mg BID] or placebo), study drug may be reduced to 2 tablets BID (ARRY 371797 [200 mg BID] or placebo) as described in this protocol. If a patient has tolerability issues at 2 tablets BID (ARRY-371797 [200 mg BID] or placebo), study drug may be further reduced to 1 tablet BID (ARRY 371797 [100 mg BID] or placebo) as described in this protocol.
If study drug is not well tolerated at any dose level, treatment will be permanently discontinued for that patient.

Study burden and risks

More than 500 adults, both healthy subjects and patients, have taken the study drugs, ARRY-371797 (PF-07265803). Side effects considered associated with ARRY-371797 in studies where patients (more than 300) have received at least 1

dose of ARRY-371797 (PF-07265803) (the study drug) are as follows:
Most common side effects (occur more than 10% of the time):
* Mouth inflammation that may be associated with ulcerations of the mouth mucous membranes.

Less common side effects (occur 1 to 20% of the time):
* Headache
* Nausea
* Vomiting
* Diarrhea
* Increased phosphokinase

Placebo
If the patients are receiving placebo there is a possibility that symptoms of their disease may return or get worse.

Blood Samples: The risks of taking blood may include fainting, pain and/or bruising. Rarely, there may be a small blood clot or infection at the site of the needle puncture.

Echocardiogram:. There have been rare occurrences (1-2%) of transient headache, back pain, flushing or nausea reported and very rare (1 in 10,000) serious allergic reactions.

Electrocardiogram: The patient will have electrodes placed on his/her chest, arms, and legs. They may have some hair shaved so the electrodes will stick to your skin. The electrodes are attached to wires which are attached to the ECG machine. During the test the patient will need to lie still while the machine records their heart*s activity. The patient should not talk during the test.

Six (6) minute walk test: The patients may experience symptoms such as fatigue, shortness of breath, leg cramps, chest pain, sweating, or other symptoms associated with this exercise.

Contacts

Public
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NL
Scientific

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Provide a signed and dated informed consent document prior to initiation of any study-related procedures. Patients under guardianship or partial guardianship will be eligible unless prohibited by local laws or by local/central ethic committees
* Age * 18 years at time of informed consent
* Patients with symptomatic lamin A/C protein (LMNA)-related cardiomyopathy Class II/III/ or Class IV defined as:
o Gene positive for a pathogenic, likely pathogenic or VUS mutation in the LMNA gene as determined by an accredited clinical laboratory
o NYHA functional class II or III that has been stable for at least 2 months.
o Evidence of cardiac impairment as determined by LVEF*50%
* Patient will have an implantable cardioverter defibrillator/cardiac resynchronization therapy defibrillator (ICD/CRT-D). ICD implanted at least 4 weeks prior to initiation of study treatment or CRT-D initiated at least 6 months prior to initiation of study intervention and defibrilation function activated at least 4 weeks prior to initiation of study intervention. Devices must have activated pacing capabilities or a separate pacemaker must be present.
* Class II/III patients must have objective functional impairment evidenced by a reduction in 6-minute walk test (6MWT);
* Stable medical and/or device therapy consistent with American Heart Association (AHA) / American College of Cardiology (ACC) or European Society of Cardiology (ESC) guidelines

* Patients must meet acceptable hematology, hepatic and renal laboratory values as specified within 35 days prior to Day 1

Exclusion criteria

* Presence of other form(s) of cardiomyopathy contributing to HF (e.g., inflammatory or infiltrative cardiomyopathy) or clinically significant cardiac anatomic abnormality (e.g., LV aneurysm), clinically significant coronary artery disease (e.g., coronary revascularization, exercise-induced angina) or uncorrected, hemodynamically significant (i.e., moderate-severe) primary structural valvular disease not due to HR, per investigator judgment
* Currently receiving or deemed at high risk of requiring chronic renal replacement therapy (e.g., hemodialysis or peritoneal dialysis) within 6 months.
* Treatment with any investigational agent(s) for HF within 35 days prior to Day 1.
* Malignancy that is active or has been diagnosed within 3 years prior to screening, except surgically curatively resected in situ malignancies or surgically cured early breast cancer, prostate cancer, skin cancer (basal cell carcinoma, squamous cell carcinoma) thyroid cancer or cervical cancer, or, with prior review of the Medical Monitor, other earlystage surgically curatively resected malignancies with less than a 20% expected 2-year recurrence rate.
* Non-cardiac condition that limits lifespan to < 1 year.
* Serum positive for hepatitis B surface antigen, viremic hepatitis C, or human immunodeficiency virus (HIV) at screening.
* Pregnancy or breastfeeding, or patients who plan to become pregnant during the duration of the trial
* Patients with an underlying condition that may impact the ability of the 6MWT to reflect changes in cardiovascular function such as: an orthopedic condition that limits walking abilities (e.g. severe arthritis), significant musculoskeletal pathology, significant chronic obstructive pulmonary disease (COPD) that limits exercise tolerance or any other condition that according to the Investigator's assessment significantly limits a patient's performance on the 6MWT independently from the patient's cardiomyopathy.
* Documented hypersensitivity/allergy or clinically significant intolerance to any component of drug product.

Study design

Design

Study phase: 3

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-05-2019
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ARRY-371797 (PF-07265803)
Generic name:	ARRY-371797 (PF-07265803)

Ethics review

Approved WMO Date:	28-05-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-01-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-02-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-07-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-07-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-09-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-10-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-04-2021
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-004310-25-NL
CCMO	NL65694.100.18